



Rego Campello, H., Parker, J. S., Perry, M. W. D., Ryberg, P., & Gallagher, T. (2016). Asymmetric Reduction of Lactam-based β -Aminoacrylates. Synthesis of Heterocyclic β 2-Amino Acids. *Organic Letters*, 18(16), 4124–4127.
<https://doi.org/10.1021/acs.orglett.6b02074>

Peer reviewed version

License (if available):
CC BY-NC

Link to published version (if available):
[10.1021/acs.orglett.6b02074](https://doi.org/10.1021/acs.orglett.6b02074)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via ACS at <http://pubs.acs.org/doi/full/10.1021/acs.orglett.6b02074#Abstract>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Asymmetric Reduction of Lactam-based β -Aminoacrylates. Synthesis of Heterocyclic β^2 -Amino Acids.

Hugo Rego Campello,^[a] Jeremy Parker,^[b] Matthew Perry,^[c] Per Ryberg,^{[d]§} and Timothy Gallagher^{[a]*}

[a] School of Chemistry, University of Bristol, Bristol, BS8 1TS UK [b] AstraZeneca, Pharmaceutical Development, Silk Road Business Park, Macclesfield, SK10 2NA UK [c] AstraZeneca, Innovative Medicines, R&I Chemistry, AstraZeneca R&D Mölndal, Peparedsleden, SE-431 83, Mölndal, Sweden [d] AstraZeneca, PR&D Södertälje, S-151 85 Södertälje, Sweden

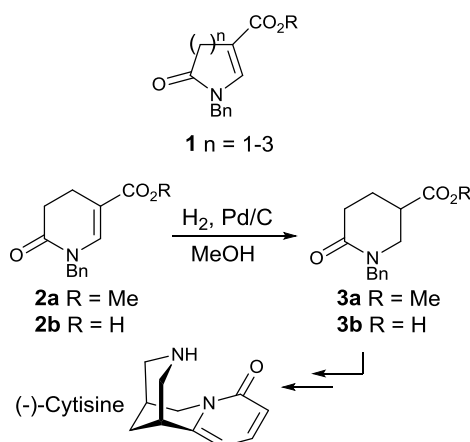
Supporting Information Placeholder

ABSTRACT: The ability to affect asymmetric reduction of heterocyclic β -aminoacrylates **1** ($n=1-3$) has been assessed with pyrrolidine and piperidone variants generating the corresponding N-heterocyclic β^2 -amino acids **3b** and **5b** with high enantioselectivity ($\geq 97\%$ ee) using a Rh/WALPHOS catalyst combination. The use of the carboxylic acid substrate was essential; the corresponding esters do undergo reduction but led to racemic products. The seven-ring azepanone variant (as the carboxylic acid **9b**) underwent reduction but only a minimal level of asymmetric induction was observed.

Functionalized and chiral N-heterocycles represent widely exploited and valuable synthetic units, where an ability to gain access to either enantiomer of the target heterocycle is often an important issue.¹ Asymmetric alkene reduction methods² are especially attractive in this area since other functional groups present in the alkene substrate e.g. a carbonyl moiety often serves to direct the catalytic reduction step; such functionality can then also be of value in terms of the synthetic flexibility inherent within the reduction product.

In terms of general C=C reduction, high enantioselectivity has been reported for a range of functionalized alkenyl substrates, such as acrylates³ and, relevant here, α - and β -amino/amidoacrylates.⁴ Similarly, cyclic enamines are effective substrates for asymmetric reduction leading to substituted 5-, 6- and 7-ring N-heterocycles.⁵

Scheme 1.



Our interest in this area has focused on reduction of an unusual class of β -amidoacrylates (i.e. lactams) of general

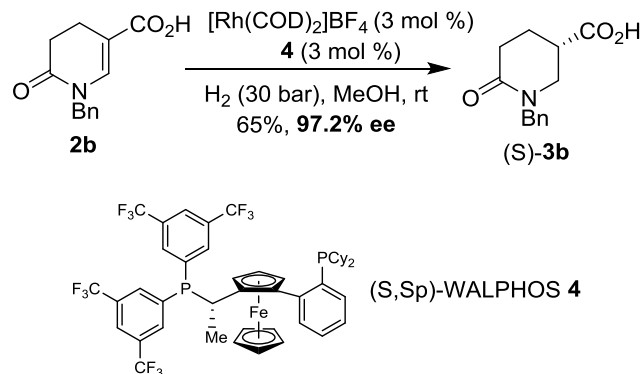
structure **1** ($n=1-3$). The potential of these systems is exemplified by lactam **2** (**1**, $n=2$); reduction of the readily available ester **2a**⁶ provides piperidone **3a** (a β^2 -amino acid derivative) which has served as a key intermediate in the synthesis of cytosine as well as of a series of cytosine variants (Scheme 1).⁷

In earlier work, we developed an asymmetric approach to cytosine by exploiting an ability to carry out a kinetic resolution of methyl ester **3a** using α -chymotrypsin (α -CHY).⁸ This provided acid (S)-**3b** ($>64\%$ ee; 48% yield), and (unreacted) ester (R)-(+)-**3a** ($>98\%$ ee; 42% yield). While useful, such resolution processes are, however, inherently inefficient. Catalytic asymmetric reduction of **2a/b**, which is a more attractive option, had been explored using standard methods reported previously for acrylates. However, these efforts enjoyed limited success; we obtained low enantioselectivities and poor conversions.⁹ One factor affecting the levels of asymmetric induction observed may link to the relative spatial disposition of the lactam carbonyl (as a potential ligand and directing group) with respect to either or both of the C=C or carboxylate functions.¹⁰

Given these limitations, the value and attractiveness of enantiomerically pure piperidinone **3a/b** in other contexts,¹¹ and the opportunity to develop a methodology applicable to a wider range of substrates, we undertook a more extensive screening program to assess the potential for the asymmetric reduction of methyl ester **2a** and carboxylic acid **2b**. A wide range of metal catalysts, ligands and reaction conditions were evaluated within AstraZeneca. Having screened a range of parameters, effective reaction conditions were identified, which are shown in Scheme 2, and asymmetric reduction of acid **2b** was achieved to product (S)-(-)-**3b** in over 97% ee with Rh catalysis in combination with (S,Sp)-WALPHOS **4** as ligand.¹²

High selectivity was observed only with carboxylic acid **2b**; methyl ester **2a** did undergo reduction but with a negligible level of enantiomeric induction under all of the different conditions evaluated. Further, the isolated (after purification) yield (65%) of (S)-**3b** is likely a result of the high pressures involved necessary to achieve reasonable conversion under which N-debenzylation appeared to begin to compete.

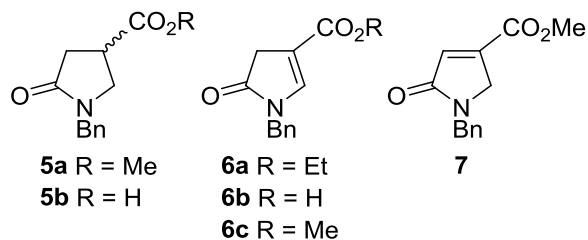
Scheme 2. Asymmetric reduction of 2b to give (S)-3b.



The stereochemical outcome of this asymmetric reduction process (in terms of generating (S)-(-)-**3b**) was established by comparison to the piperidinone products obtained from enzymatic kinetic resolution. In this earlier work we had obtained as the unreacted enantiomer, ester (R)-(+)-**3a** in high enantiomeric excess which we had then converted to (unnatural) (+)-cytisine.

We have further explored the scope of this reduction methodology and examined the viability of the corresponding pyrrolidine and azepane-based lactams **1** ($n=0$ and 2 respectively) given that, alongside piperidone **2**, these would provide a homologous series of enantiomerically-enriched, functionalized and synthetically versatile N-heterocyclic units.

In the case of the pyrrolidine variant, then the enzymatic kinetic resolution of (\pm)-**5a** (to provide access to enriched ester (R)-(-)-**5a** and acid (S)-(+)-**5b**) has been reported.¹³ This earlier work provided us with a basis of a later structural assignment but two potential reduction substrates needed to be considered: the β -aminoacrylates **6a/b**¹⁴ (the $\Delta^{4,5}$ -lactam, analogous to **2a/b**) and the corresponding $\Delta^{3,4}$ -isomer (incorporating a fumarate subunit), previously reported as the methyl ester **7**.¹⁵



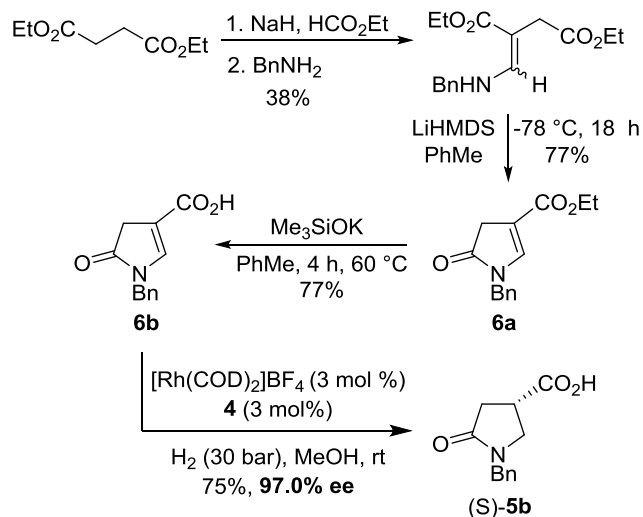
The synthesis of β -aminoacrylate **6a/b** we have developed is shown in Scheme 3 and is based on formylation of diethyl succinate followed by enamine formation (using benzylamine), cyclization of which was best carried out under strongly basic conditions. Given our experience in the piperidinone series, we focused attention on the use of the

corresponding carboxylic acid **6b** as the reduction substrate but the conversion of ester **6a** to acid **6b** proved to be surprisingly difficult; product degradation under standard conditions appeared to be facile.¹⁶ Optimal conditions developed are shown in Scheme 3 and, once isolated, acid **6b** is crystalline, stable and easily handled.

Reduction of acid **6b** followed a very similar course to that of **2b** and the (S)-(+)-carboxylic acid **5b** was isolated in 75% yield and in 97% ee. The configuration of **5b** was established by comparison with optical rotation data reported for this compound derived by enzymatic resolution¹³ and clearly **2b** and **6b** undergo asymmetric reduction in the same sense as one another under these Rh/WALPHOS conditions.

We were interested in the behavior of the isomeric lactam **7** under reduction conditions, recognizing that C=C isomerization could be involved in the reduction of β -aminoacrylates such as **6b**. However, our attempts to reproduce the route reported to **7** failed to give the product claimed;¹⁵ see Supporting Information. In our hands the only product obtained these conditions was methyl ester **6c** (i.e. the $\Delta^{4,5}$ -lactam isomer) which was isolated in 70% yield.

Scheme 3. Synthesis of 6a and 6b; asymmetric reduction of 6b



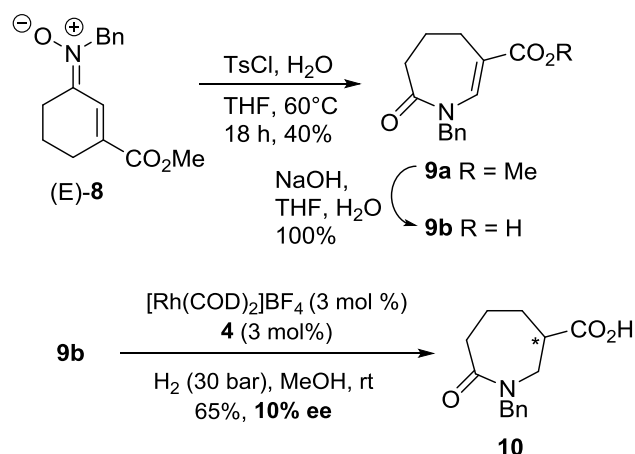
The azepane variant **9** was prepared using a nitron-based Beckmann rearrangement (Scheme 4) which was based on the earlier work of both Barton^{17a} and Ward.^{17b} To avoid a problematic separation of isomeric lactam products, it was critical to isolate the individual nitron isomers **8** (isolated as a 3:1 mixture of E/Z isomers) prior to rearrangement. In this way azepene **9a** was obtained in 40% yield and converted efficiently to the corresponding acid **9b**.

Reduction of **9b**, under the conditions applied to **1b** and **5b**, provided the azepane **10** but in 10% ee and the absolute configuration of the predominant product was not established. This was a surprising result given the relatively small structural modification involved, and further work will be needed to probe the mechanism by which this set of substrates interacts with the Rh/ligand complex.¹⁸

Given that both pyrrolidinone **5a** and piperidone **3a** are viable substrates for kinetic resolution using α -chymotrypsin (α -CHY), we have evaluated methyl ester **11** under these conditions (Scheme 5). Ester **11** was obtained in

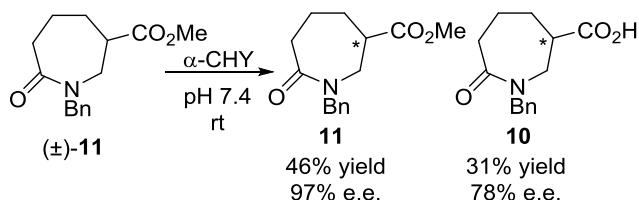
85% yield by hydrogenation of **9a** (see Supporting Information).

Scheme 4. Synthesis of 9a and 9b; asymmetric reduction of 9b



At pH 7.4, racemic **11** underwent selective hydrolysis and the corresponding acid **10** was isolated in 31% yield and 78% ee and the unreacted ester **11** was recovered in 46% yield and 97% ee (as assessed by chiral HPLC).¹⁹ We have not assigned the absolute configurations of these products and this process has not been optimized further in terms of yields and enantiomeric purities.

Scheme 5. Enzymatic kinetic resolution of (±)-11



In summary, we have shown that an unusual but synthetically useful class of heterocyclic β -aminoacrylates undergo efficient asymmetric reduction with a Rh-WALPHOS catalyst combination. This process works efficiently for the pyrrolidinone and piperidinone carboxylic acid substrates **6b** and **2b** respectively but the level of enantiomeric selectivity dramatically diminished in the case of the seven-ring azepine substrate **9b**.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds, and the x-ray crystallographic structure determination of (S)-**3b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

*E-mail: T.Gallagher@bristol.ac.uk

§Current address for PR: Ferring Pharmaceuticals, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

We thank Dr Mairi Haddow and Dr Hazel Sparkes for crystallographic determination of **3b**, the University of Bristol for a postgraduate fellowship (to HRC) and AstraZeneca for partial financial support and access to catalyst screening/optimization facilities.

REFERENCES

- (1) The ability to access selectively either enantiomer of a target (e.g. bioactive) molecule is widely appreciated, and methods of “measuring” different complexity descriptors, including chirality, have been reported: (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Lovering, F. *Med. Chem. Commun.* **2013**, *4*, 515. (c) Zayit, A.; Pinsky, M.; Elgavi, H.; Dryzum, C.; Avnir, D. *Chirality* **2011**, *23*, 17.
- (2) For reviews of asymmetric alkene reduction, see: (a) Chi, Y.-X.; Tang, W.-J.; Zhang, X. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P.A., Ed.; Wiley-VCH: Weinheim, 2005; pp 1-31. (b) Genet, J. P. In *Modern Reduction Methods*; Andersson, P. G.; Munslow, I. J., Eds.; Wiley-VCH: Weinheim, 2008; pp 3-38. Hartwig, J. In *Organotransition Metal Chemistry*, 1st ed.; University Science Books: Sausalito, 2010, Ch. 15 pp 575-665.
- (3) High selectivity has been reported for the asymmetric reduction of acrylates: (a) Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 7189. (b) Yamada, I.; Yamaguchi, M.; Yamagishi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3339. (c) Uemura, T.; Zhang, X. Y.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510. (d) Yamada, I.; Ohkouchi, M.; Yamaguchi, M.; Yamagishi, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1869. (e) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4209. (f) Khumsubdee, S.; Burgess, K. *ACS Catalysis* **2013**, *3*, 237. (g) Song, S.; Zhu, S.-F.; Li, Y.; Zhou, Q.-L. *Org. Lett.* **2013**, *15*, 3722.
- (4) The synthesis of β -amino acids (including via reduction methods to provide β^2 -derivatives) has been reviewed, see: Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Grošelj, U.; Zass, E. *Synthesis* **2009**, 1. Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656. Rh-mediated asymmetric hydrogenation of acrylates, β -amino acrylates and β^2 -dehydroamino esters has been reported: (a) Gonsalves, A.; Bayon, J. C.; Pereira, M. M.; Serra, M. E. S.; Pereira, J. P. R. *J. Organomet. Chem.* **1998**, *553*, 199. (b) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2015. (c) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701. (d) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309. (e) Hoen, R.; Tiemersma-Wegman, T.; Procuranti, B.; Lefort, L.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2007**, *5*, 267. (f) Qiu, L.; Prashad, M.; Hu, B.; Prasad, K.; Repic, O.; Blacklock, T. J.; Kwong, F. Y.; Kok, S. H. L.; Lee, H. W.; Chan, A. S. C. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16787. (g) Bisset, A. A.; Shiibashi, A.; Desmond, J. L.; Dishington, A.; Jones, T.; Clarkson, G. J.; Ikariya, T.; Wills, M. *Chem. Commun.* **2012**, *48*, 11978. More recently, the Rh- and Ru-mediated asymmetric hydrogenation of N-acyl β -aminoacrylic acids (the acyclic variant of the systems described here) to provide β^2 -(arylated)amino acids has been reported: Remarchuk, T.; Babu, S.; Stults, J.; Zanotti-Gerosa, A.; Roseblade, S.; Yang, S.; Huang, P.; Sha, C.; Wang, Y. *Org. Process Res. Dev.* **2014**, *18*, 135.
- (5) For a review of the asymmetric hydrogenation of enamines, see: Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. Studies have reported high selectivity for the asymmetric

- hydrogenation of enamines and cyclic enamines: (a) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366. (b) Zhou, Q.-L.; Xie, J.-H. In *Stereoselective Formation of Amines*, Li, W.; Zhang, X., Eds. Springer-Verlag: Berlin, 2013; pp 75-101.
- (6) Ester **2a** is available on a multi-gram scale: Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575. Subsequent conversion of ester **2a** to acid **2b** was carried out in essentially quantitative yield using NaOH/H₂O/THF.
- (7) (a) Botuha, C.; Galley, M. S. C.; Gallagher, T., *Org. Biomol. Chem.* **2004**, *2*, 1825. (b) Hirschhäuser, C.; Haseler, C. A.; Gallagher, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 5162. For different approaches to structurally-related piperidinones, see Struth, F. R.; Hirschhäuser, C. *Eur. J. Org. Chem.* **2016**, 958. Khong, D. T.; Pamarthy, V. S.; Gallagher, T.; Judeh, Z. M. A. *Eur. J. Org. Chem.* **2016**, 3084.
- (8) Gray, D.; Gallagher, T., *Angew. Chem. Int. Ed.* **2006**, *45*, 2419.
- (9) We utilized Ru-based methods based on BINAP and Me-Duphos (MeOH, 20-50 °C) under both hydrogenation and transfer hydrogenation conditions. The enantioselectivities observed for reduction of ester **2a** and acid **2b** using Ru[(R,R)-Me-Duphos](COD))BF₄ were respectively 24% and 10% ee, but chemical conversions were only of the order of 25%. Ester reduction of ester **2a** was also carried out to assess the potential of the corresponding allylic alcohol as a substrate under asymmetric hydrogenation conditions. This alcohol was extremely labile and over-reduction to form the corresponding 5-methyl lactam was observed (Botuha, C.; Gallagher, T. unpublished work).
- (10) For asymmetric reduction of heterocyclic enamines carrying an N-Boc moiety (i.e. a carbonyl director on the periphery rather than integral to the heterocycle), see: Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155. Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056.
- (11) Lactams **3** and **5** provide multi-point, spiro-fused heterocyclic scaffolds: Hirschhäuser, C.; Parker, J. S.; Perry, M. W. D.; Haddow, M. F.; Gallagher, T. *Org. Lett.* **2012**, *14*, 4846.
- (12) We used (S)-1-((S)-2-[2-(dicyclohexylphosphino)phenyl]ferrocenyl)ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine (CAS: 849925-22-0), both enantiomers of which are commercially available.
- (13) The enzymatic resolution of ester **5a** has been reported: Felluga, F.; Pitacco, G.; Prodan, M.; Pricl, S.; Visintin, M.; Valentin, E. *Tetrahedron: Asymmetry* **2001**, *12*, 3241.
- (14) Pyrrolidinone **6a** has been reported using a very different approach to that shown in Scheme 3, see: Dubinina, G. G.; Chain, W. J. *Tetrahedron Lett.* **2011**, *52*, 939.
- (15) Lactam **7** (the $\Delta^{3,4}$ -isomer) was of interest because of the possibility that alkene isomerisation (**6**→**7**) may occur prior to C=C reduction. The synthesis of ester **7** was reported by Amri: Besbes, R.; Villiéras, M.; Amri, H. *Indian J. Chem.* **1997**, *36B*, 5. However, in our hands, this route gave only the $\Delta^{4,5}$ -isomer isomer ester **6c**; see Supporting Information for characterization and for references to related structures. We suggest that the original authors mis-assigned the structure of their final product as **7** rather than the β -amino acrylate **6c**.
- (16) Extensive decomposition of **6a** occurred under standard ester hydrolysis conditions. Optimal conditions involved use TMSOK (Lovrić, M.; Cepanec, I.; Litvić, M.; Bartolinčić, A.; Vinković, V. *Croat. Chem. Acta* **2007**, *80*, 109). Once isolated, acid **6b** is a stable, colorless solid.
- (17) (a) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1764. (b) Prager, R. H.; Raner, K. D.; Ward, A. D. *Aust. J. Chem.* **1984**, *37*, 381. Under Beckmann rearrangement conditions nitron (**Z**)-**8** gave a complex mixture of products within which we were unable to isolate **9a**. Reaction of (*E*)-**8** provided a much less complicated mixture of products from which **9a** was isolated in 40% yield.
- (18) The steep drop-off in % ee with the seven-ring substrate **9b** was surprising, but **9b** has not been screened separately against a bank of metals/ligands. Incorporating three sp³ centers, molecular models suggest that **9b** is significantly more puckered than either the 5- or 6-ring variants which may affect the relative stability of the diastereomeric substrate-metal complexes. Nicolaou has reported the asymmetric reduction of N-acyl heterocyclic dehydroamino esters (to give α -amino esters) where the opposite trend i.e. increasing enantioselectivity with increasing ring size was observed. However, it is probable that these substrates involve a chelated metal complex involving the N-acyl moiety which is not possible with the substrates we report here. Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757.
- (19) Enantiomeric purities reported were determined by chiral HPLC using racemates as standards.

